Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study

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Summary

Background **Tocilizumab, a monoclonal antibody directed against the interleukin-6 receptor, has been proposed to mitigate the cytokine storm syndrome associated with severe COVID-19. We aimed to investigate the association between tocilizumab exposure and hospital-related mortality among patients requiring intensive care unit (ICU) support for COVID-19.**

Methods **We did a retrospective observational cohort study at 13 hospitals within the Hackensack Meridian Health network (NJ, USA). We included patients (aged ≥18 years) with laboratory-confirmed COVID-19 who needed support in the ICU. We obtained data from a prospective observational database and compared outcomes in patients who received tocilizumab with those who did not. We applied a multivariable Cox model with propensity score matching to reduce confounding effects. The primary endpoint was hospital-related mortality. The prospective observational database is registered on ClinicalTrials.gov, NCT04347993.**

Findings **Between March 1 and April 22, 2020, 764 patients with COVID-19 required support in the ICU, of whom 210 (27%) received tocilizumab. Factors associated with receiving tocilizumab were patients' age, gender, renal function, and treatment location. 630 patients were included in the propensity score-matched population, of whom 210 received tocilizumab and 420 did not receive tocilizumab. 358 (57%) of 630 patients died, 102 (49%) who received tocilizumab and 256 (61%) who did not receive tocilizumab. Overall median survival from time of admission was not reached (95% CI 23 days–not reached) among patients receiving tocilizumab and was 19 days (16–26) for those who did not receive tocilizumab (hazard ratio [HR] 0·71, 95% CI 0·56–0·89; p=0·0027). In the primary multivariable Cox regression analysis with propensity matching, an association was noted between receiving tocilizumab and decreased hospital-related mortality (HR 0·64, 95% CI 0·47–0·87; p=0·0040). Similar associations with tocilizumab were noted among subgroups requiring mechanical ventilatory support and with baseline C-reactive protein of 15 mg/dL or higher.**

Interpretation **In this observational study, patients with COVID-19 requiring ICU support who received tocilizumab had reduced mortality. Results of ongoing randomised controlled trials are awaited.**

Funding None.

Introduction

Worldwide more than 20 million individuals have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus causing COVID-19. As of Aug 13, 2020, almost 750 000 deaths have been reported globally.[1] Infection causes destruction of alveolar epithelial cells, activation of the innate immune system, and dysregulation of adaptive immune responses, including release of proinflammatory cytokines and chemokines. This so-called cytokine storm might have an important role in the progression to respiratory and multiorgan failure.[2,3]

Tocilizumab, a recombinant monoclonal antibody against the interleukin (IL)-6 receptor, has been used to mitigate the cytokine release syndrome associated with chimeric antigen receptor (CAR) T-cell therapy and has been proposed as a potential therapy for the cytokine storm syndrome associated with severe COVID-19 pneumonia based on small phase 2 studies.[4–10] Preliminary unpublished results of the phase 2 French CORIMUNO-TOCI trial, involving 129 patients, noted a reduction in mortality and requirement for mechanical ventilation in patients who received tocilizumab.[11] A large multinational randomised placebo-controlled phase 3 trial evaluating tocilizumab in the treatment of severe COVID-19 pneumonia is underway (NCT04320615). Additional trials of tocilizumab are also ongoing.

Without data from randomised trials, observational studies can provide useful early insights into effective treatment strategies.[12,13] However, treatment allocations are often based on the clinician's judgment in an observational study, rather than random assignment, which increases

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Research in context

Evidence before this study

We searched PubMed, Embase, Cochrane Reviews, and Scopus from Jan 1 to April 22, 2020, with the terms "tocilizumab" AND "COVID" OR "coronavirus". This search identified an increasing interest in the rationale to use tocilizumab in patients with severe COVID-19 and several case reports or small observational studies reporting a benefit with its use. Preliminary results from France of the phase 2 CORIMUNO-TOCI trial showed a reduction in mortality and requirement for mechanical ventilation in patients who received tocilizumab. A large, multinational, randomised, placebo-controlled phase 3 trial evaluating tocilizumab for treatment of patients with severe COVID-19-related pneumonia is underway (NCT04320615).

Added value of this study

We did a retrospective, observational cohort study to investigate mortality in patients with severe COVID-19 needing support in the intensive care unit and receiving tocilizumab. Use of tocilizumab was associated with improvement in median overall survival from time of admission compared with patients who did not receive tocilizumab. In a post-hoc analysis, patients with baseline C-reactive protein levels of 15 mg/dL or higher were most likely to show an associated improved survival with tocilizumab, whereas no association was seen in patients with lower levels of C-reactive protein.

Implications of all the available evidence

Our findings support the preliminary findings of the CORIMUNO-TOCI trial and show an association between C-reactive protein levels, tocilizumab, and survival, potentially suggesting that tocilizumab might exert its best effects among patients with COVID-19 progressing to an inflammatory state. Current evidence supports continued evaluation of tocilizumab in a randomised trial for patients with severe COVID-19.

the risk of bias and does not account for known and unknown risk factors. Thus, causal inferences on effectiveness of treatments are challenging, but confounding effects can be partly mitigated via statistical methods.[14]

Understanding the limitations of observational studies, but with the urgency to assess potential therapeutic approaches, the 13 hospitals within the Hackensack Meridian Health network (NJ, USA) considered off-label use of tocilizumab in patients with severe SARS-CoV-2 infection who required intensive care unit (ICU) support. To evaluate treatments for COVID-19, we established an observational database using an integrated electronic health record system (EPIC; Verona, WI, USA). We aimed to compare outcomes between patients with COVID-19 in the ICU who received tocilizumab and those who did not receive tocilizumab.

For more on **Research Electronic Data Capture** see https://www.project-redcap.org/

Methods

Study design and patients

We did a retrospective, observational, multicentre cohort study at the 13 hospitals within the Hackensack Meridian Health network. We derived data from electronic health records of patients with COVID-19 who received ICU support. Our selection criteria were adult patients (aged ≥18 years) with a positive SARS-CoV-2 diagnosis by RT-PCR who were hospitalised at one of Hackensack Meridian Health's 13 hospitals during the study period and required ICU support. We excluded patients who were pregnant and those who were participating in a clinical therapeutic trial. Patients receiving tocilizumab for chronic rheumatological conditions were not excluded.

We obtained Institutional Review Board (IRB) approval for access to the prospective observational database. The requirement for patient's informed consent was waived by the IRB because this project represented a non-interventional study using routinely gathered data for secondary research reasons.

Procedures

We obtained data from Hackensack Meridian Health's electronic health record, which is used throughout the hospital network. Hospitalised patients were flagged by the electronic health record if SARS-CoV-2 PCR tests were positive. These reports generated by the electronic health record served as our eligible cohort sample. Demographics, clinical characteristics, treatments, and outcomes were manually abstracted by research nurses and clinicians from the John Theurer Cancer Center at Hackensack Meridian Health. Assignment of patients to our data team occurred in real time but was not randomised. Data abstracted by the team were entered, using Research Electronic Data Capture. Quality control was done by two of us (AI and SLG).

Demographic information was gathered on an electronic face sheet. Gender and race or ethnicity were self-reported. Academic centres were defined as quaternary referral centres with accredited residency, fellowship, and medical student programmes. Comorbidities were defined as diagnosed before hospitalisation for COVID-19. History of cardiovascular disease, chronic lung disease, cancer, renal failure, and rheumatological disease was abstracted from provider notes or medical history sections within the electronic health record. If not listed, the patient's comorbidities were recorded as absent. ICU support included all patients receiving mechanical ventilator support, patients hospitalised within a dedicated ICU, and patients with assignment to ICU staff regardless of geographical placement (overflow during pandemic conditions). Patients who received remdesivir were treated in the context of a clinical study and were excluded. Lopinavir was not on

institutional formulary or used for COVID-19 treatment and, if used in another context, data were not gathered. Presenting clinical information was abstracted from thorough review of unstructured notes and structured data. Hospital re-admissions were counted as the same admission, with baseline data used from the initial hospitalisation. If multiple positive or indeterminate results were found in a patient's record for SARS-CoV-2, the first initial positive test was used as the date of diagnosis.

Exposure to tocilizumab was defined as receipt of the drug as found in the electronic health record. If no evidence of tocilizumab administration was found, we recorded that the patient had not received tocilizumab. Off-label use of tocilizumab within the Hackensack Meridian Health network was guided by the Pharmacy and Therapeutics Committee, with recommendations to consider treatment in patients with evidence of acute respiratory distress syndrome on mechanical ventilation, or worsening oxygenation with high oxygen requirements (80–100%) on high-flow nasal cannula or 15 L non-rebreather mask. Symptoms had to be present for 7 days and documentation of informed consent was needed. However, the final decision to use tocilizumab was at the discretion of the treating clinician. The Pharmacy and Therapeutics Committee suggested one intravenous dose of 400 mg tocilizumab. A randomised placebo-controlled trial of tocilizumab was available at one academic centre within the Hackensack Meridian Health network (Hackensack University Medical Center, Hackensack, NJ, USA). The rationale for selection of the 400 mg intravenous dose of tocilizumab was based on published work from China,[6] albeit preclinical and not peer reviewed at that time, which showed improved oxygenation using a dose of tocilizumab around 4 mg/kg. A second dose of tocilizumab was permitted at the point of worsening oxygenation (eg, increased oxygen [O_2] requirement, high-flow O_2) and before mechanical ventilation, with administration at the treating clinician's discretion.

Outcomes

The primary outcome measure was hospital-related mortality, which was identified on chart review as a note from the treating clinician announcing time of death during hospitalisation or if the electronic health record labelled the patient as deceased after hospital discharge. Cause of death was identified using the electronic health record by identifying the most immediate cause or causes recorded. Respiratory cause of death included any hypoxic condition related to COVID-19. Cardiac cause of death included cardiac arrest, myocardial infarction, or arrhythmia. Infectious cause of death included bacterial sepsis or secondary infections not including COVID-19. Other cause of death included multiorgan failure in addition to alternative causes.

Preplanned secondary outcome measures were changes in inflammatory markers (C-reactive protein, IL-6, ferritin, and D-dimer), change in oxygenation requirements, infections (defined as bacteraemia or pneumonia with positive sputum culture), and use of vasopressors.

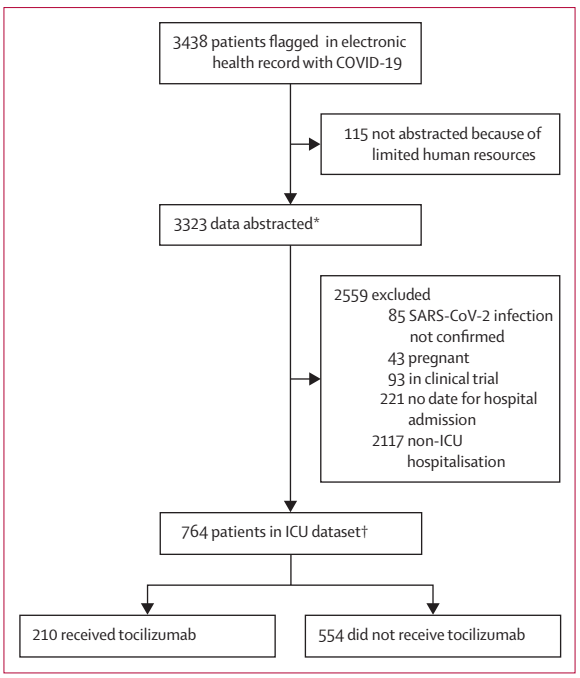

Figure 1: **Patient sampling strategy**
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ICU=intensive care unit. *Convenience sampling was done when assigning patients to our data team, and sampling bias is possible. †Follow-up until final study cutoff date of May 22, 2020.

Statistical analysis

Demographic and clinical variables of tocilizumab treatment were summarised using median (IQR) for continuous variables and by frequency (%) for categorical variables. Differences in the median and distribution of demographic and clinical variables between patients who received tocilizumab and those who did not were compared using Mood's median test for continuous variables and Fisher's exact test or Pearson's χ^2 test for categorical variables.

To analyse overall survival we plotted Kaplan-Meier curves and did the log-rank test to compare outcomes of patients who received tocilizumab and did not receive this drug. The index date used for overall survival was the date of hospital admission. Adjusted Cox proportional hazards regression models were fitted to estimate the association between tocilizumab use and overall survival, using clinically likely confounders including age, gender, diabetes, chronic obstructive pulmonary disease (COPD) or asthma, hypertension, cancer, renal failure, obesity, oxygenation less than 94%, quick Sequential Organ Failure Assessment (qSOFA) score, use of steroids, C-reactive protein 15 mg/dL or higher, and intubation or mechanical ventilator support. To account for immortal time bias in the group receiving tocilizumab, time to tocilizumab treatment after admission was also adjusted. When the goodness-of-fit model was not

satisfied, we further reduced all these confounders using stepwise variable selection.[15] Hazard ratios (HRs) and 95% CIs were summarised.

To reduce confounding effects secondary to imbalances in receiving tocilizumab treatment inherent to a retrospective cohort study, we did propensity score matching.

	Unmatched patients (n=764)			Propensity score-matched patients (n=630)*		
	No tocilizumab (n=554)	Tocilizumab (n=210)	p value	No tocilizumab (n=420)	Tocilizumab (n=210)	p value
Demographics						
Age, years	68 (58–78)	62 (53–71)	0·0003	65 (56–74)	62 (53–71)	0·20
Gender	..	..	0·0037	..	..	0·082
Female	207 (37%)	55 (26%)	..	139 (33%)	55 (26%)	..
Male	347 (63%)	155 (74%)	..	281 (67%)	155 (74%)	..
Race or ethnic origin	..	..	0·84	..	..	0·43
African American	48 (9%)	19 (9%)	..	31 (7%)	19 (9%)	..
White	308 (56%)	114 (54%)	..	229 (55%)	114 (54%)	..
Hispanic	109 (20%)	36 (17%)	..	93 (22%)	36 (17%)	..
Other	75 (14%)	32 (15%)	..	54 (13%)	32 (15%)	..
Missing data	14 (3%)	9 (4%)	..	13 (3%)	9 (4%)	..
Nursing home resident	79 (14%)	11 (5%)	0·0004	42 (10%)	11 (5%)	0·047
Hospital setting	..	..	<0·0001	..	..	<0·0001
Non-academic	321 (58%)	178 (85%)	..	232 (55%)	178 (85%)	..
Academic	233 (42%)	32 (15%)	..	188 (45%)	32 (15%)	..
Former or current smoker	128 (23%)	39 (19%)	0·090	94 (22%)	39 (19%)	0·11
Comorbidities						
Comorbidity count†	..	..	0·025	..	..	0·12
0	73 (13%)	30 (14%)	..	68 (16%)	30 (14%)	..
1	129 (23%)	68 (32%)	..	99 (24%)	68 (32%)	..
2	132 (24%)	50 (24%)	..	106 (25%)	50 (24%)	..
≥3	220 (40%)	62 (30%)	..	147 (35%)	62 (30%)	..
Diabetes	218 (39%)	77 (37%)	0·41	158 (38%)	77 (37%)	0·86
COPD or asthma	96 (17%)	30 (14%)	0·28	61 (15%)	30 (14%)	>0·99
Hypertension	347 (63%)	122 (58%)	0·18	254 (60%)	122 (58%)	0·61
Coronary disease	103 (19%)	29 (14%)	0·11	73 (17%)	29 (14%)	0·30
Stroke	28 (5%)	11 (5%)	>0·99	16 (4%)	11 (5%)	0·41
Heart failure	55 (10%)	16 (8%)	0·33	35 (8%)	16 (8%)	0·88
Arrhythmia	64 (12%)	13 (6%)	0·023	42 (10%)	13 (6%)	0·13
Cancer	78 (14%)	20 (10%)	0·091	49 (12%)	20 (10%)	0·50
Renal failure	64 (12%)	12 (6%)	0·015	27 (6%)	12 (6%)	0·86
Rheumatological disorder	22 (4%)	5 (2%)	0·38	14 (3%)	5 (2%)	0·63
Body-mass index ≥30 kg/m²	200 (36%)	76 (36%)	>0·99	154 (37%)	76 (36%)	0·93
Presentation and disease severity						
Fever	381 (69%)	161 (77%)	0·039	300 (71%)	161 (77%)	0·18
Cough	368 (66%)	152 (72%)	0·16	290 (69%)	152 (72%)	0·46
Shortness of breath	398 (72%)	169 (80%)	0·019	308 (73%)	169 (80%)	0·072
Gastrointestinal	106 (19%)	48 (23%)	0·31	87 (21%)	48 (23%)	0·61
Altered mental state	93 (17%)	29 (14%)	0·32	57 (14%)	29 (14%)	>0·99
Oxygenation <94%	267 (48%)	102 (49%)	0·93	206 (49%)	102 (49%)	>0·99
qSOFA score	..	..	0·026	..	..	0·48
0	218 (39%)	75 (36%)	..	168 (40%)	75 (36%)	..
1	183 (33%)	88 (42%)	..	154 (37%)	88 (42%)	..
2	50 (9%)	9 (4%)	..	24 (6%)	9 (4%)	..
3	7 (1%)	1 (<1%)	..	1 (<1%)	1 (<1%)	..
Missing data	96 (17%)	37 (18%)	..	73 (17%)	37 (18%)	..

(Table 1 continues on next page)

	Unmatched patients (n=764)			Propensity score-matched patients (n=630)*		
	No tocilizumab (n=554)	Tocilizumab (n=210)	p value	No tocilizumab (n=420)	Tocilizumab (n=210)	p value
(Continued from previous page)						
Treatment						
Steroids	235 (42%)	97 (46%)	0·40	191 (45%)	97 (46%)	0·84
Hydroxychloroquine	462 (83%)	199 (95%)	<0·0001	355 (85%)	199 (95%)	0·0001
Azithromycin	287 (52%)	141 (67%)	<0·0001	213 (51%)	141 (67%)	<0·0001
Hydroxychloroquine and azithromycin	259 (47%)	137 (65%)	<0·0001	193 (46%)	137 (65%)	<0·0001
Initial vital signs						
FiO_2, %	100 (90–100)	100 (100–100)	>0·99	100 (85–100)	100 (100–100)	<0·0001
PEEP, cm H_2O	10 (8–14)	10 (8–14)	0·78	10 (10–15)	10 (8–14)	0·89
Vasopressor use	221 (40%)	88 (42%)	0·93	176 (42%)	88 (42%)	0·79
PaO_2:FiO_2	..	..	0·80	..	..	0·88
<100	125 (23%)	54 (26%)	..	103 (25%)	54 (26%)	..
100 to <200	69 (12%)	30 (14%)	..	56 (13%)	30 (14%)	..
200 to <300	19 (3%)	5 (2%)	..	14 (3%)	5 (2%)	..
≥300	14 (3%)	5 (2%)	..	12 (3%)	5 (2%)	..
Missing data	327 (59%)	116 (55%)	..	235 (56%)	116 (55%)	..
Intubation or ventilator	488 (88%)	198 (94%)	0·015	389 (93%)	198 (94%)	0·50
Initial laboratory test						
Ferritin, ng/mL	1067·5 (541·1–2070·5)	1123·7 (477·9–1720·5)	0·93	1123·3 (571·2–2107·5)	1123·7 (548·6–1720·5)	>0·99
C-reactive protein, mg/dL	15·7 (7·1–25·3)	14·3 (7·7–24·2)	0·39	15·2 (7·7–24·9)	14·3 (7·7–24·2)	0·48
Interleukin-6, pg/mL	19 (7–50)	29 (9–96)	0·056	18·5 (7·0–49·75)	29 (9–96)	0·049
D-dimer, µg/mL	0·86 (0·86–2·90)	1·63 (0·86–4·48)	0·0001	0·98 (0·86–3·11)	1·63 (0·86–4·48)	0·016
Outcomes						
Extubated	291 (53%)	119 (57%)	0·33	233 (55%)	119 (57%)	0·80
Discharged	365 (66%)	135 (64%)	0·79	281 (67%)	135 (64%)	0·72

Data are n (%) or median (IQR). COPD=chronic obstructive pulmonary disorder. qSOFA=quick Sequential Organ Failure Assessment. FiO_2=fractional concentration of oxygen in inspired air. PEEP=positive end-expiratory pressure. PaO_2=partial pressure of arterial oxygen. *13 variables were used for propensity score matching: age, gender, diabetes, COPD or asthma, hypertension, cancer, renal failure, obesity, oxygenation <94%, qSOFA score, use of steroids, C-reactive protein >15 mg/dL, and intubation or mechanical ventilator support. Hosmer and Lemeshow goodness-of-fit test, p=0·51. †Number of comorbidities from diabetes, COPD or asthma, hypertension, coronary disease, cerebrovascular disease, heart failure, arrhythmia, cancer renal failure, rheumatological disorder, and body-mass index ≥30 kg/m^2.

Table 1: **Baseline characteristics of unmatched and propensity score-matched patients**

First, we calculated a propensity score of receiving tocilizumab treatment for each patient using multivariable logistic regression with the confounders age, gender, diabetes, COPD or asthma, hypertension, cancer, renal failure, obesity, oxygenation less than 94%, qSOFA score, use of steroids, C-reactive protein 15 mg/dL or higher, and intubation or mechanical ventilator support. Goodness of fit of the multivariable logistic model was examined using the Hosmer-Lemeshow test. We then used non-parametric nearest-neighbour matching of propensity scores to generate a matched cohort in a 1:2 ratio to pair a patient with tocilizumab treatment to two patients who did not receive tocilizumab, using the *MatchIt* package in *R*.[16,17]

In the propensity score-matched population, we repeated the adjusted Cox modelling done in the unmatched population. Moreover, we compared the medians of each biomarker between patients who received tocilizumab and those who did not receive tocilizumab at days 1, 3, 7, and 14 using Mood's median test. Subgroup analyses were done of patients who received mechanical ventilator support and who were older than 65 years and aged 65 years or younger, using the same datasets. Missing data for categorical confounders with more than 10% missing data were coded as a missing data category and were included in all analyses. Completely observed data-only analyses were followed. We assessed the sensitivity of HR estimates to varying sets of confounders, including the propensity score as a covariate in the unmatched model and including confounders chosen by stepwise selection.

We judged statistical significance when the p value was less than 0·05. For subgroup analyses, Bonferroni correction (type I error of 0·01) was applied and 99% CIs were also reported (appendix pp 9–13). For secondary outcome analyses, no multiplicity correction was applied. All statistical analyses were done using *R* version 3.4.

See Online for appendix

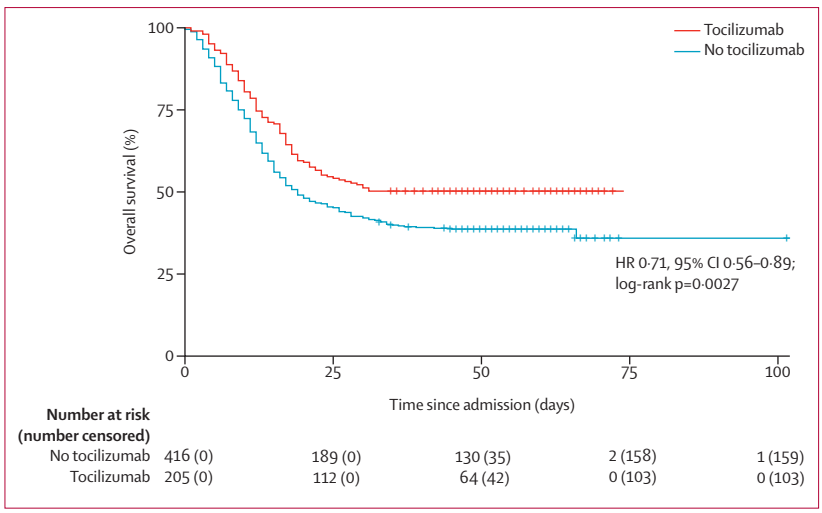

Figure 2: **Overall survival among propensity score-matched patients**
Among 630 propensity score-matched patients, overall survival data were not available for four patients who did not receive tocilizumab and five patients who did receive tocilizumab. The Kaplan-Meier curve is based on observed data (n=621). HR=hazard ratio.

The prospective observational database is registered on ClinicalTrials.gov, NCT04347993.

Role of the funding source

This study received no external funding. AI, SLG, NB, JA, MM, BAS, and SW had access to raw data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 1 and April 22, 2020, 3438 patients were flagged in the electronic health record with a diagnosis of COVID-19. To reduce sampling bias, data were abstracted for 3323 (97%) patients. The remaining 115 (3%) patients were not abstracted because of limited human resources during the peak of the COVID-19 pandemic in New Jersey. 764 (23%) patients needed support in the ICU (figure 1). No patients were known to have been receiving tocilizumab for chronic rheumatological conditions.

The distribution of baseline characteristics according to tocilizumab exposure is shown in table 1. In the unmatched population, 210 patients who received at least one infusion of tocilizumab were significantly younger than 554 patients who did not receive tocilizumab (median age 62 years [IQR 53–71] *vs* 68 years [58–78]; p=0·0003). 220 (40%) of 554 patients who did not receive tocilizumab had three or more comorbidities, compared with 62 (30%) of 210 patients who received tocilizumab. A propensity score-matched population was constructed of 630 patients, 210 who received at least one infusion of tocilizumab and 420 who did not receive tocilizumab. The propensity score-matched population was well balanced except with respect to nursing home residents (11 [5%] of 210 who received tocilizumb *vs* 42 [10%] of 420 who did not receive tocilizumab; p=0·047) and patients treated at non-academic hospitals (178 [85%] of 210 *vs* 232 [55%] of 420; p<0·0001).

Of 210 patients in the propensity score-matched population who received tocilizumab, 206 (98%) received 400 mg flat dosing, two (1%) received 8 mg/kg, and two (1%) received other doses; 185 (88%) received one infusion and 25 (12%) received a second infusion. Tocilizumab was administered a median of 9 days (IQR 6–12) after the start of patient-reported symptoms, a median of 3 days (1–7) from the date of hospitalisation, and a median of 0 days (0–2) from the date of ICU support.

Patients were followed up until May 22, 2020. Median follow-up of patients in the propensity score-matched population was 22 days (IQR 11–53). 358 (57%) of 630 patients died, 102 (49%) of 210 who received tocilizumab and 256 (61%) of 420 who did not receive tocilizumab. Causes of death among the 102 patients who received tocilizumab were respiratory (n=57), cardiac (n=21), infectious (n=3), and other causes (n=10); for 11 patients the cause of death was not apparent. Causes of death among the 256 patients who did not receive tocilizumab were respiratory (n=127), cardiac (n=57), infectious (n=15), and other causes (n=20); for 37 patients the cause of death was not apparent. Median overall survival from time of admission for patients receiving tocilizumab was not reached (95% CI 23 days–not reached) and for those who did not receive tocilizumab it was 19 days (16–26; HR 0·71, 95% CI 0·56–0·89; p=0·0027; figure 2). In the unmatched cohort, there was a similar finding in median overall survival in patients receiving tocilizumab (not reached, 95% CI 23 days–not reached) versus those not receiving tocilizumab (17 days, 15–20; p=0·0002; overall survival data were not available for 12 patients in the unmatched population; appendix p 2). After adjusting for time from initial tocilizumab treatment, the findings were also similar (appendix p 3). In the primary multivariable Cox regression analysis with propensity score matching, exposure to tocilizumab was associated with lower hospital-related mortality (HR 0·64, 95% CI 0·47–0·87; p=0·0040; table 2). Sensitivity analyses showed similar associations (appendix pp 6–8).

In the subgroup of 587 patients in the propensity score-matched population who required mechanical ventilation, patients who received tocilizumab had reduced hospital-related mortality (HR 0·63, 95% CI 0·46–0·85; p=0·0029; table 3; appendix p 9). Hospital-related mortality was slightly reduced in patients younger than 65 years (HR 0·64, 95% CI 0·44–0·94; p=0·023), but not in those aged 65 years or older (0·71, 0·48–1·04; p=0·079; table 3; appendix pp 10–11).

Dose intensity of steroid treatment was not obtained in the study. However, use of steroids was not associated with decreased hospital-related mortality in the overall propensity score-matched population (HR 0·94, 95% CI 0·73–1·21; p=0·63; table 2), or among any of the patient subpopulations (table 3; appendix p 10). Sensitivity

analyses using different sets of confounder adjustment show similar results (appendix pp 6–8).

Inspired by findings of a non-peer-reviewed tocilizumab study,[18] a post-hoc analysis was done of C-reactive protein (≥15 mg/dL or <15 mg/dL). C-reactive protein data were available for 558 (89%) of 630 patients in the propensity score-matched population. A reduction of C-reactive protein with tocilizumab exposure was noted at 3, 7, and 14 days after initiation of treatment in the propensity score-matched population (appendix p 4). Among 286 patients with C-reactive protein levels of 15 mg/dL or higher, tocilizumab exposure was associated with decreased hospital-related mortality (HR 0·48, 95% CI 0·30–0·77; p=0·0025; table 3; appendix p 12). However, among 272 patients with baseline C-reactive protein levels less than 15 mg/dL, little protective association was seen between tocilizumab and hospital-related mortality (HR 0·92, 95% CI 0·57–1·48; p=0·73; table 3; appendix p 13).

A transient increase in IL-6 concentration was noted at days 3 and 7 among patients who received tocilizumab. No associations were identified for amounts of D-dimer, ferritin, or lactate dehydrogenase (appendix p 4).

In the propensity score-matched population, 18 (9%) of 210 patients who received tocilizumab and 33 (8%) of 420 who did not receive tocilizumab developed bacteraemia during ICU support. Positive sputum cultures were identified in 25 (12%) and 30 (7%) patients, respectively. Overall secondary bacterial infections were recorded in 36 (17%) of 210 patients who received tocilizumab and 54 (13%) of 420 patients who did not receive tocilizumab. Cardiac vasopressor support was used equally, regardless of receipt of tocilizumab (88 [42%] of 210 and 176 [42%] of 420, respectively). No association was reported in reduction of fractional concentration of O_2 in inspired air requirements and receipt of tocilizumab at day 1 after treatment, and little association was seen in changes of positive end-expiratory pressure or partial pressure of O_2 in arterial blood values (appendix p 5).

	Unmatched multivariable Cox model (n=727)		Propensity score-matched multivariable Cox model (n=616)	
	Estimated HR (95% CI)	p value	Estimated HR (95% CI)	p value
Tocilizumab, yes *vs* no	0·65 (0·48–0·87)	0·0040	0·64 (0·47–0·87)	0·0040
Age, ≥65 years *vs* <65 years	2·10 (1·68–2·62)	<0·0001	2·00 (1·58–2·53)	<0·0001
Gender, female *vs* male	0·71 (0·58–0·88)	0·0015	0·68 (0·53–0·86)	0·0015
Diabetes, yes *vs* no	1·16 (0·95–1·41)	0·15	1·19 (0·96–1·49)	0·12
COPD or asthma, yes *vs* no	1·07 (0·83–1·38)	0·61	1·02 (0·76–1·38)	0·88
Hypertension, yes *vs* no	1·32 (1·06–1·65)	0·014	1·44 (1·13–1·84)	0·0031
Cancer, yes *vs* no	1·17 (0·89–1·53)	0·27	1·17 (0·86–1·61)	0·32
Renal failure, yes *vs* no	1·16 (0·87–1·56)	0·32	1·41 (0·96–2·09)	0·084
Body-mass index				
≥30 kg/m² *vs* <30 kg/m²	1·06 (0·85–1·32)	0·59	1·04 (0·82–1·32)	0·74
Missing *vs* no	1·26 (0·79–2·01)	0·33	1·02 (0·60–1·73)	0·95
Oxygenation <94%				
Yes *vs* no	1·09 (0·88–1·35)	0·43	1·13 (0·89–1·44)	0·30
Missing *vs* no	0·43 (0·20–0·89)	0·024	0·46 (0·21–1·00)	0·051
qSOFA score				
1 *vs* 0	1·29 (1·02–1·61)	0·031	1·19 (0·93–1·53)	0·16
2 *vs* 0	1·51 (1·07–2·13)	0·019	1·37 (0·88–2·15)	0·17
3 *vs* 0	2·40 (1·04–5·51)	0·040	0·96 (0·13–7·07)	0·97
Missing *vs* 0	1·90 (0·96–3·76)	0·065	1·88 (0·91–3·88)	0·089
Steroids				
Yes *vs* no	0·89 (0·71–1·11)	0·30	0·94 (0·73–1·21)	0·63
Missing *vs* no	1·22 (0·87–1·69)	0·24	1·32 (0·90–1·93)	0·16
C-reactive protein ≥15 mg/dL				
Yes *vs* no	1·11 (0·89–1·37)	0·36	1·15 (0·91–1·44)	0·25
Missing *vs* no	2·12 (1·60–2·79)	<0·0001	2·11 (1·49–2·98)	<0·0001
Intubation, yes *vs* no	3·39 (2·04–5·65)	<0·0001	8·78 (2·79–27·61)	0·0002
Time to tocilizumab treatment	1·02 (0·98–1·06)	0·40	1·02 (0·98–1·06)	0·37

Goodness-of-fit test: p=0·42 for unmatched model; p=0·31 for propensity score-matched model. HR=hazard ratio. COPD=chronic obstructive pulmonary disorder. qSOFA=quick Sequential Organ Failure Assessment.

Table 2: **Multivariable Cox regression**

Discussion

In this multicentre observational study of patients with COVID-19 requiring ICU support, receipt of tocilizumab was associated with a reduction in hospital-related mortality. Moreover, patients who required mechanical ventilator support and those younger than 65 years showed a favourable reduction in hospital-related mortality with tocilizumab. Furthermore, in a post-hoc analysis, a reduction in mortality was seen in patients who received tocilizumab who had concentrations of C-reactive protein of 15 mg/dL or higher. Therefore, tocilizumab seems to be among the first potentially successful treatments for patients with severe COVID-19 requiring ICU support, pending confirmation by an ongoing randomised trial (NCT04320615).

The cytokine storm noted in patients with late-stage SARS-CoV-2 infection is typically the primary cause of death.[19] The aberrant host immune response includes increased concentrations in plasma of proinflammatory cytokines, including IL-6, which trigger further organ tissue damage.[6,7] In view of similarities between the cytokine storm syndrome of COVID-19 and the cytokine release syndrome associated with CAR T-cell therapy, a rationale for IL-6-directed blockade is easily drawn.[20,21]

We identified an association between concentrations of C-reactive protein, tocilizumab, and overall survival, potentially suggesting that tocilizumab could exert its effects among patients whose COVID-19 illness is progressing to an inflammatory state. Patients who received tocilizumab showed a reduction in C-reactive protein levels at 3, 7, and 14 days after administration of tocilizumab compared with patients who did not receive tocilizumab. The potential beneficial association of tocilizumab was seen only in patients with C-reactive protein of 15 mg/dL or higher at baseline. C-reactive protein and IL-6 have been reported to be the most sensitive and reliable factors in distinguishing disease severity and prognosis.[22] IL-6 has been shown to

	Estimated hazard ratio (95% CI)	p value
Mechanical ventilation (n=587)		
Tocilizumab, yes *vs* no	0·63 (0·46–0·85)	0·0029
Age, ≥65 years *vs* <65 years	1·96 (1·56–2·48)	<0·0001
Gender, female *vs* male	0·67 (0·53–0·86)	0·0013
Diabetes, yes *vs* no	1·18 (0·95–1·48)	0·14
COPD or asthma, yes *vs* no	1·04 (0·77–1·40)	0·81
Hypertension, yes *vs* no	1·44 (1·13–1·84)	0·0036
Cancer, yes *vs* no	1·19 (0·87–1·63)	0·29
Renal failure, yes *vs* no	1·44 (0·97–2·13)	0·068
Body-mass index	..	..
≥30 kg/m² *vs* <30 kg/m²	1·05 (0·83–1·34)	0·67
Missing *vs* no	1·02 (0·60–1·74)	0·95
Oxygenation <94%	..	..
Yes *vs* no	1·17 (0·92–1·49)	0·21
Missing *vs* no	0·46 (0·21–1·01)	0·054
qSOFA score	..	..
1 *vs* 0	1·18 (0·92–1·52)	0·19
2 or 3 *vs* 0	1·35 (0·87–2·10)	0·18
Missing *vs* 0	1·89 (0·92–3·91)	0·085
Steroids	..	..
Yes *vs* no	0·92 (0·72–1·18)	0·50
Missing *vs* no	1·31 (0·90–1·93)	0·16
C-reactive protein ≥15 mg/dL	..	..
Yes *vs* no	1·15 (0·91–1·44)	0·25
Missing *vs* no	2·11 (1·50–2·99)	<0·0001
Time to tocilizumab treatment	1·02 (0·98–1·06)	0·31
Age <65 years (n=307)		
Tocilizumab, yes *vs* no	0·64 (0·44–0·94)	0·023
Gender, female *vs* male	0·57 (0·37–0·90)	0·015
Hypertension, yes *vs* no	1·54 (1·07–2·21)	0·020
Cancer, yes *vs* no	1·82 (1·02–3·22)	0·041
Renal failure, yes *vs* no	2·19 (1·12–4·25)	0·021
qSOFA score	..	..
1 *vs* 0	1·73 (1·16–2·59)	0·0074
2 or 3 *vs* 0	2·55 (1·29–5·03)	0·0069
Missing *vs* 0	1·36 (0·68–2·72)	0·39
Steroids	..	..
Yes *vs* no	0·68 (0·45–1·02)	0·061
Missing *vs* no	0·61 (0·34–1·10)	0·10
Age ≥65 years (n=312)		
Tocilizumab, yes *vs* no	0·71 (0·48–1·04)	0·079
Gender, female *vs* male	0·74 (0·55–0·99)	0·042
Diabetes, yes *vs* no	1·22 (0·93–1·60)	0·15
COPD or asthma, yes *vs* no	0·89 (0·61–1·31)	0·56
Hypertension, yes *vs* no	1·39 (1·00–1·91)	0·047
Cancer, yes *vs* no	1·09 (0·74–1·61)	0·65
Renal failure, yes *vs* no	1·32 (0·81–2·15)	0·27
Body-mass index	..	..
≥30 kg/m² *vs* <30 kg/m²	0·94 (0·69–1·28)	0·69
Missing *vs* no	0·85 (0·43–1·68)	0·64

(Table 3 continues in next column)

	Estimated hazard ratio (95% CI)	p value
(Continued from previous column)		
Oxygenation <94%	..	..
Yes *vs* no	1·13 (0·83–1·54)	0·44
Missing *vs* no	0·46 (0·18–1·19)	0·11
qSOFA score	..	..
1 *vs* 0	1·07 (0·78–1·47)	0·68
2 or 3 *vs* 0	1·24 (0·69–2·24)	0·48
Missing *vs* 0	1·86 (0·82–4·20)	0·14
Steroids	..	..
Yes *vs* no	1·10 (0·80–1·51)	0·56
Missing *vs* no	1·93 (1·15–3·24)	0·013
C-reactive protein ≥15 mg/dL	..	..
Yes *vs* no	1·17 (0·88–1·56)	0·27
Missing *vs* no	2·31 (1·46–3·65)	0·0003
Intubation, yes *vs* no	2·62 (0·81–8·50)	0·11
Time to tocilizumab treatment	1·01 (0·96–1·06)	0·83
C-reactive protein ≥15 mg/dL (n=286)		
Tocilizumab, yes *vs* no	0·48 (0·30–0·77)	0·0025
Age, ≥65 years *vs* <65 years	1·97 (1·39–2·78)	0·0001
Gender, female *vs* male	0·84 (0·59–1·19)	0·32
Diabetes, yes *vs* no	1·30 (0·93–1·80)	0·12
COPD or asthma, yes *vs* no	0·80 (0·44–1·46)	0·47
Hypertension, yes *vs* no	1·17 (0·82–1·67)	0·39
Cancer, yes *vs* no	1·20 (0·71–2·01)	0·50
Renal failure, yes *vs* no	1·85 (0·96–3·57)	0·066
Body-mass index	..	..
≥30 kg/m² *vs* <30 kg/m²	0·99 (0·69–1·42)	0·96
Missing *vs* no	1·21 (0·56–2·62)	0·62
Oxygenation <94%	..	..
Yes *vs* no	1·14 (0·78–1·64)	0·50
Missing *vs* no	0·17 (0·04–0·81)	0·026
qSOFA score	..	..
1 *vs* 0	1·07 (0·73–1·56)	0·74
2 or 3 *vs* 0	1·22 (0·64–2·33)	0·55
Missing *vs* 0	2·88 (0·70–11·86)	0·14
Steroids	..	..
Yes *vs* no	0·85 (0·59–1·22)	0·37
Missing *vs* no	1·28 (0·69–2·38)	0·43
Intubation, yes *vs* no	8·56 (1·18–62·03)	0·034
Time to tocilizumab treatment	1·04 (0·98–1·10)	0·20
C-reactive protein <15 mg/dL (n=272)		
Tocilizumab, yes *vs* no	0·92 (0·57–1·48)	0·73
Age, ≥65 years *vs* <65 years	1·83 (1·28–2·62)	0·0010
Gender, female *vs* male	0·59 (0·41–0·85)	0·0041
Diabetes, yes *vs* no	1·32 (0·94–1·86)	0·11
Hypertension, yes *vs* no	1·89 (1·26–2·85)	0·0023
Intubation, yes *vs* no	9·14 (2·24–37·33)	0·0021
Time to tocilizumab treatment	0·97 (0·91–1·04)	0·43

COPD=chronic obstructive pulmonary disease. qSOFA=quick Sequential Organ Failure Assessment.

***Table 3*: Subgroup analyses in the propensity score-matched population**

regulate C-reactive gene expression in transgenic animals and serves as one of the necessary drivers of increased C-reactive protein.[23,24]

Several reports have described a correlation between concentrations of ferritin, D-dimer, and lactate dehydrogenase with severity of COVID-19.[25,26] IL-1 blockade has also been reported to reduce COVID-19 mortality, and a study from the Groupe Hospitalier Paris Saint-Joseph showed a significant decrease in risk for ICU admission, mechanical ventilation, or death with use of the IL-1 receptor antagonist anakinra.[27] Recognition of inflammatory markers or other cytokine-directed treatment could have important implications for treatment selection.

Tocilizumab was administered early in the ICU course, typically on the day of admission for ICU support, and a median of 9 days since the start of self-reported symptoms. Whether earlier administration of tocilizumab at the time of hospital admission might improve outcomes and decrease overall resource use requires study.

In the RECOVERY trial,[28] steroid use was associated with improvement in survival among patients with severe SARS-CoV-2 infection. Among all patients in our propensity score-matched population, steroid use was not associated with a reduction in hospital-related mortality. Baseline mortality for intubated patients in the ICU in our study was significantly higher than in the RECOVERY study (268 [64%] of 420 who did not receive tocilizumab in our study *vs* 164 [41%] of 400 without dexamethasone in RECOVERY), suggesting possible differences in patient populations.

We did not note an associated increase in secondary bacteraemia with tocilizumab treatment. The frequency of secondary bacterial infections was 17% in patients who received tocilizumab and 13% in those who did not. Our infection rates seem low for a cohort of critically ill patients. However, we administered a lower dose of tocilizumab (a 400 mg flat dose as a one-time infusion in most patients) by contrast with 8 mg/kg dosing used in the ongoing, international, randomised placebo-controlled trial. An increase in use of hydroxychloroquine was noted in patients who received tocilizumab compared with those who did not receive tocilizumab, which we do not believe had a relevant effect on our findings because most observational studies have not reported a benefit for hydroxychloroquine among hospitalised patients, despite potentially some activity in early SARS-CoV-2 infection.[29]

Our observational study has limitations. First, observational studies cannot draw causal inferences because of inherent known and unknown confounders. We attempted to adjust for known confounders using our propensity score-matched approach. We also did several sensitivity analyses, including models with the propensity score as a covariate, models with stepwise selection of covariates based on the Akaike information criterion, and models selected by Lasso. Second, misclassifications of data are possible because we manually abstracted structured and unstructured data from electronic health records. Missing data were addressed by creating a category for missing in the multivariable Cox regression analysis for the key (categorical) confounders with more than 10% missing data. We also did a sensitivity analysis when we excluded patients with missing information (appendix pp 7–8). Our study focused on patients in the US state of New Jersey, limiting applicability to other geographical regions, although this US state's population is diverse and the Hackensack Meridian Health network included 13 hospitals with differing treatment protocols. Further, we acknowledge the possibility of indication bias, because it was not always clear why some patients were given tocilizumab or not. Patients considered to have severe SARS-CoV-2 infection by institutional guidelines were permitted to receive tocilizumab at the discretion of their treating clinician. Our cohort had a high prevalence of comorbidities and were older, in the setting of an overburdened health-care system, and represented the peak incidence of SARS-CoV-2 infection, which probably skewed our mortality rates higher than those reported in other cohorts. Finally, we acknowledge the possibility of sampling bias since we obtained data from a convenience sample in attempts to do a rapid investigation during a pandemic.

Tocilizumab exposure among patients with severe SARS-CoV-2 infection requiring ICU support was associated with a reduction in hospital-related mortality. These data could help to inform current clinical practice while randomised controlled trials are underway.

Contributors

SLG, AI, and NB had the idea for and designed the study. JA, SW, AHG, ISS, and LSK contributed to study design. NB, AI, RCG, and SLG did the literature search. NB, AI, JA, and SW prepared the figures. All authors contributed to data collection and data analysis. NB, AI, JA, SW, and SLG contributed to data interpretation. NB, AI, JA, RCG, SW, DSS, and SLG contributed to writing of the report.

Declaration of interests

RCG is the primary investigator for the Roche Genentech-COVACTA study at Hackensack University Medical Center. SM reports consultancy for Regional Cancer Care Associates and Hackensack Meridian Health, outside of the submitted work. EH reports consultancy from Regional Cancer Care Associates and Hackensack Meridian Health, outside of the submitted work. DSS reports equity in COTA. AHG is a primary investigator for Genentech-Hoffman La Roche, during the conduct of the study; reports personal fees and research funding as study investigator from Acerta, AstraZeneca, Celgene, Kite Pharma, Elsevier's PracticeUpdate Oncology, Gilead, Medscape, MJH Associates, OncLive Peer Exchange, Physicians Education Resource, and Xcenda, outside of the submitted work; and reports research funding as study investigator from Constellation, Infinity, Infinity Verastem, Janssen, Karyopharm, and Pharmacyclics, outside of the submitted work. ALP reports equity in COTA. LSK is a co-investigator for the Roche Genentech-COVACTA study at Hackensack University Medical Center. SLG reports equity in COTA. All other authors declare no competing interests.

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